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(54) Title: PROSTAGLANDIN DERIVATIVES FOR THE TREATMENT OF GLAUCOMA OR OCULAR HYPERTENSION

(57) Abstract

Use of derivatives of a diastereomer of prostaglandin F_{2alpha}, viz. 11 epi, for the manufacture of compositions for the treatment of glaucoma or ocular hypertension.

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Prostaglandin derivatives for the treatment of glaucoma or ocular hypertension

The invention is concerned with the use of derivatives of a specific diastereomer of prostaglandin F_{2alpha}, viz. 11 epi, for the treatment of glaucoma or ocular hypertension. The invention furthermore also relates to ophthalmological compositions containing an active amount of these prostaglandin derivatives.

Glaucoma is an ocular disorder characterized by elevated intraocular pressure, excavation of the optic nerve head and gradual loss of the vision field. An abnormally high intraocular pressure will have a generally detrimental effect on the eye; and there are clear indications that this is probably the main factor causing degenerative changes of the retina in glaucoma patients. However, the pathophysiological mechanism underlying open-angle glaucoma is still unknown. If not treated successfully the disease will usually proceed to blindness sooner or later, its course towards that stage being characterized by a slow but progressive loss of vision.

The intraocular pressur IOP (abbr. of intraocular pressure) is usually defined by the formula

$$IOP = P_e + F \times R \qquad (1)$$

where P_e is the pressure in the episcleral veins, generally considered to be around 9 mm Hg; F is a measure of aqueous humor flow rate; and R is the resistance to aqueous humor outflow through the trabecular meshwork and adjacent tissue into Schlemm's canal.

Another path along which the aqueous humor may flow, in addition to the Schlemm's canal path, is via the ciliary muscle into the suprachoroidal space and then out of the eye through the sclera. This uveoscleral path has been described

by e.g. Bill (1975). The pressure gradient along this path is very insignificant as compared to the gradient in the first mentioned case over the interior wall of Schlemm's canal and adjacent tissue. The flow-limiting step along the uveoscleral path is believed to reside in the flow from the anterior chamber into the suprachoroidal space.

A more complete formula is the following:

$$IOP = P_e + (F_t - F_u) \times R \qquad (2)$$

where P_e and R have the same meanings as above; F_t represents the total outflow of aqueous humor; and F_u represents that portion thereof which goes via the uveoscleral path.

In humans the IOP will normally be within the range of from 12 to 22 mm Hg. At higher values, e.g. exceeding 22 mm Hg, there is a risk that the eye may be affected. In a special form of glaucoma, the so-called low-tension glaucoma, lesions will occur at intraocular pressure levels which are generally regarded as physiological. Possibly this may be due to an increased pressure sensitivity of the eye of such an individual. Also the opposite type of phenomenon is known, i.e. some individuals may have an abnormally high intraocular pressure without any noticeable distinct defects in their vision field or optic nerve head. Such conditions are usually named "ocular hypertension".

Glaucoma treatments may be given by means of drugs, laser or surgery. In the case of drug treatments, the purpose is to achieve a reduction of either the flow (F) or the resistance (R), which will result in a lower IOP according to formula (1) above; or alternatively the purpose may be to increase the flow via the uveoscleral path - which too will be a means of lowering the pressure as can be seen from formula (2). Cholinergic agonists like for instance pilocarpine reduce the intraocular pressure mainly by increasing the outflow through Schlemm's canal.

Interest in prostaglandins as IOP- reducing substances has been growing substantially for quite some time; the mechanism underlying their effect probably being an increased uveoscleral outflow (Crawford et al. 1987, and Nilsson et al. 1987). These substances on the other hand do not appear to have any effect on either the formation of aqueous humor or the conventional outflow through Schlemm's canal (Crawford et al. 1987).

The use of prostaglandins and derivatives thereof is described in for example US 4599353 and EP 87103714.9.

With respect to the practical usefulness of some of the previously described prostaglandins and derivatives as suitable as drugs for treating glaucoma or ocular hypertension, a limiting factor is their property of causing superficial irritation and vasodilatation in the conjunctiva. It is probable moreover that prostaglandins have an irritant effect on the sensory nerves of the cornea. Thus local side effects will arise in the eye already when the amounts of prostaglandin administered are quite small - that is, already when the doses are lower than those that would be desirable for achieving maximum pressure reduction. It has thus been found for instance that for this reason it is clinically impossible to use PGF_{2alpha}-1-isopropyl ester in the amount that would give maximum pressure reduction. Prostaglandins being naturally occurring autacoids are very potent pharmacologically and affect both sensory nerves and smooth muscle of the blood vessels. Since the effects caused by administrations of PGF_{2alpha} and its esters to the eye comprise in addition to pressure reduction also irritation and hyperemia (increased blood flow) the doses currently practicable in clinical tests are necessarily very low. The irritation experienced when PGF_{2alpha} or its esters are applied consists mainly in a feeling of grittiness or of having a foreign body in one's eye, this being usually accompanied by increased lacrimation.

We have now found, surprisingly, that a diastereomer of prostaglandin PGF_{2alpha}, viz. 11 epi, will lower the eye pressure without causing any substantial irritation. In this stereoisomer the hydroxyl at carbon atom 11 lies above the cyclopentane ring. This isomer of PGF_{2alpha} has been known heretofore; it is a metabolite of PGD_2 (Liston and Roberts 1985, Pugliese et al. 1985). The 11 epi PGF_{2alpha}-1-isopropyl ester which as far as we know has not been described heretofore will give rise to hyperemia in the conjunctiva to about the same extent as the PGF_{2alpha}-1-isopropyl ester, but this will not involve any hazard or inconvenience as long as irritation problems are absent.

The present invention thus relates to 1-alkyl or 1-alkylaryl esters of 11 epi PGF_{2alpha} to be used for treating glaucoma or ocular hypertension. The alkyl chain of the 1-alkyl esters comprises 1-10, preferably 1-7, and especially 1-5 carbon atoms. The 1-alkylaryl esters have an aryl group monosubstituted by a lower alkyl chain. This lower alkyl chain has 1-5 carbon atoms. In an embodiment currently preferred, the 11 epi PGF_{2alpha}-1-isopropyl ester is used.

Furthermore, the invention relates to compositions for the treatment of glaucoma or ocular hypertension, said compositions containing an effective intraocular pressure reducing amount of at least one 11 epi PGF_{2alpha}-1-ester defined as above, in an ophthalmologically compatible vehicle. The term "effective amount" here means that the composition contains about 0.1-10 µg, especially 1-10 µg of the active substance.

The ophthalmologically compatible vehicle which may be employed for preparing compositions of this invention comprises aqueous solutions as e.g. physiological salines, oil solutions or ointments. The vehicle furthermore may contain ophthalmologically compatible preservatives such as e.g. benzalkonium chloride, surfactants like e.g. Tween® 80, liposomes or polymers, for example methyl cellulose, polyvinyl

alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for the purpose of increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

The invention moreover relates to a method for treating glaucoma or ocular hypertension. The method consists in contacting a composition as aforesaid with the eye in order to reduce eye pressure and to maintain said pressure on a reduced level. The composition contains 0.1-10 /ug, especially 1-10 /ug, of the active substance i.e. the 11 epi PGF_{2alpha} ester; the treatment may advantageously be carried out in that one drop of the composition, corresponding to about 30 /ul, is administered about 1 to 4 times to the patient's eye.

The invention is illustrated by means of the following non-limitative examples.

Experiments

1. Synthesis of 11 epi PGF_{2alpha}-1-isopropyl ester

20 mg (0,056 mmol) of 11 epi PGF_{2alpha} (Cayman Chemicals, US) were dissolved in acetone at room temperature. To this solution were added 54.5 mg (0.336 mmol) of diazabicycloundecene (DBu) and 76.15 mg (0.448 mmol) of propyl iodide, whereupon the mixture was left to stand at room temperature for 8 hours. The solvent was removed in vacuo, the residue then being dissolved in 50 ml of ethyl acetate, washed with 20 ml of water, 20 ml of 3 % citric acid and 5 % sodium hydrogen carbonate; thereafter the organic phase was dried over sodium sulfate. The solvent was removed in vacuo and

the residue was purified by means of column chromatography on silica gel, with ethyl acetate - acetone (1:1) as the eluent. The yield of the product was about 76 %, and its purity was tested by means of thin layer chromatography and NMR.

2. Preparation of eye drops containing 11 epi PGF_{2alpha}-1-isopropyl ester

PGF_{2alpha}-1-isopropyl ester or 11 epi PGF_{2alpha}-1-isopropyl ester produced according to Example 1 was mixed with an eye drop solution containing 0.5 % Tween 80 as a micelle-forming substance plus 0.01 % benzalkonium chloride as a preservative to 50 /ug/ml concentration. Healthy volunteers received in one of their eyes one drop (30 /ul) containing 1.5 /ug of either PGF_{2alpha}-1-isopropyl ester or 11 epi PGF_{2alpha}-1-isopropyl ester, and in the other eye one drop of the vehicle without any added prostaglandin compound, this other eye being the contralateral control eye. Feelings of irritation and hyperemia in the conjunctiva were then recorded during a period of two hours. Eye pressures were measured 2, 4, 6 and 8 hours after administration of 11 epi PGF_{2alpha}-1-isopropyl ester, and 4 and 8 hours after administration of PFG_{2alpha}-1-isopropyl ester. With prostaglandin eye drops the maximum pressure reducing effect in the eye is expected to be achieved 6-8 hours after administration of the preparation.

Eye pressure was measured by means of applanation tonometry, either with Godmann's applanation tonometer or with a pneumatonometer (Digilab Mode -30RT), after anesthesia of the cornea with oxybuprocaine drops or with a mixture of oxybuprocaine and fluorescein. Results could be read only after measurements were complete.

Feelings of irritation in the eye i.e. grittiness were classified by scores ranging from 0 to 3 where 0 = no irritation, 1 = slightly irritating, 2 = moderately irritating and 3 = highly irritating. Hyperemia in the conjunctiva was assessed only visually.

The results of the tests performed on healthy volunteers with 11 epi PGF_{2alpha}-1-isopropyl ester and PGF_{2alpha}-1-isopropyl ester are set forth in Tables I and II. Application of 1.5 /ug of 11 epi PGF_{2alpha} administered as the 1-isopropyl ester in a particular vehicle and application of 1.5 /ug PGF_{2alpha} administered as the 1-isopropyl ester in the same vehicle resulted in 1-2 mm Hg pressure reduction in normotensive individuals 4 to 8 hours after application, as compared to the control eye (Table I). The pressure reduction was statistically significant on a $P<0.05$ to $P<0.02$ level.

This pressure reduction may appear to be a small one, but it is a well-known fact that normotensive individuals will generally show fairly little reaction in response to pressure reducing drugs. This is true also of e.g. pilocarpine and timolol. As can be seen from Table II, irritation after application of 1.5 /ug 11 epi PGF_{2alpha} was felt to be considerably less than the irritation felt upon application of 1.5 /ug PGF_{2alpha} when each had been administered in the form of its 1-isopropyl ester. This is very important from a clinical point of view, since it may thus be espected that the drug will be used in doses high enough to bring about a maximal reduction of eye pressure.

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TABLE 1

Prostaglandin	n	0 h Exp. (mmHg)	0 h Contr. (mmHg)	0 h Diff. (mmHg)	2 h Exp. (mmHg)	2 h Contr. (mmHg)	2 h Diff. (mmHg)	4 h Exp. (mmHg)	4 h Contr. (mmHg)	4 h Diff. (mmHg)	6 h Exp. (mmHg)	6 h Contr. (mmHg)	6 h Diff. (mmHg)	8 h Exp. (mmHg)	8 h Contr. (mmHg)	8 h Diff. (mmHg)
11 epi PGF_{2alpha}-1-isopropyl ester	5	14.7 ± 2.2	14.5 ± 1.6	± 0.3 ± 0.7	13.7 ± 2.0	15.1 ± 1.5	-1.4 ± 0.7	13.4 ± 1.6	14.5 ± 1.4	-1.1 ± 0.4 x)	11.8 ± 2.0	13.8 ± 1.2	-1.9 1.1	12.1 ± 1.0	13.3 ± 1.0	-1.2 ± 0.3 xx)
PGF_{2alpha}-1-isopropyl ester	6	-	-	-	-	-	-	15.6 ± 0.8	17.4 ± 1.3	-1.8 ± 0.7 x)	-	-	-	15.0 ± 0.4	16.9 ± 1.3	-1.9 ± 1.1

Eye pressure reducing effect of 11 epi PGF_{2alpha}-1-isopropyl ester and PGF_{2alpha}-1-isopropyl ester on normotensive individuals after local application of a 30 µl eye drop containing 1.5 µg of the active substance calculated as free acid. Contralateral control eyes were treated with vehicle alone.

x) = $p > 0.05$

xx) = $p > 0.02$

TABLE II

	Time after application				
Prostaglandin	15'	30'	45'	60'	120'
11 epi-PGF_{2alpha} -1-isopropyl ester	0.4 ± 0.2 xxx)	0.2 ± 0.2 xxx)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
PGF_{2alpha} -1-isopropyl ester	1.5 ± 0.4	1.7 ± 0.2	1.8 ± 0.2	1.3 ± 0.2	0.5 ± 0.2

xxx) $p < 0.01$

Feeling of pain (grittiness) in the eye of normotensive individuals after local application of 1.5 /ug 11 epi PGF_{2alpha}-1-isopropyl ester or 1.5 /ug PGF_{2alpha}-1-isopropyl ester calculated as free acid. A scale of scores ranging from 0 to 3 was used for pain assessment.

Claims

1. 1-alkyl or 1-alkylaryl esters of 11 epi PGF_{2alpha} for use in the treatment of glaucoma or ocular hypertension.

2. 11 epi PGF_{2alpha}-1-alkyl esters according to claim 1, characterized in that the alkyl chain has 1-10, preferably 1-7, and especially 1-5 carbon atoms.

3. 11 epi PGF_{2alpha}-1-alkylaryl esters according to claim 1, characterized in that the aryl group is monosubstituted by a lower alkyl group having 1-5 carbon atoms.

4. 11 epi PGF_{2alpha}-1-isopropyl ester for use in the treatment of glaucoma or ocular hypertension.

5. Composition for the local treatment of glaucoma or ocular hypertension, characterized by containing an effective intraocular pressure reducing amount of an 11 epi PGF_{2alpha}-1-ester according to any of claims 1-4 in an ophthalmologically compatible vehicle.

6. Composition according to claim 5, characterized in that the ophthalmologically compatible vehicle is a physiological saline, an oil solution or an ointment, and that it optionally contains ophthalmologically compatible preservatives, surfactants, liposomes or polymers.

7. The use of 1-alkyl or 1-alkylaryl esters of 11 epi PGF_{2alpha} for the manufacture of a composition for the local treatment of glaucoma or ocular hypertension.

8. The use according to claim 7 in which the 11 epi PGF_{2alpha} ester is an 1-alkyl ester with 1-10, preferably 1-7, carbon atoms in the alkyl chain.

9. The use according to claim 8 in which the 11 epi PGF_{2alpha} ester is the 1-isopropylester.

10. Treatment of glaucoma or ocular hypertension by contacting the eye with a composition containing an effective intraocular pressure reducing amount of an 1-alkyl or 1-alkylaryl ester of 11 epi PGF_{2alpha}.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE88/00515

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC [4]

C07C 177/00, A61K 31/557

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 2-4	C07C 177/00; A61K 31/557
US Cl	560:121; 514:573

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No [13]
X	PROSTAGLANDINS, Vol. 11, No. 1, January 1976, pages 77-84. W.L. MILLER et al: "Relative biological activity of certain prostaglandins and their enantiomers". Table 1	1-6
A	EP,A,0 093 380 (THE TRUSTEES OF COLUMBIA UNIVERSITY) 9 November 1983 Page 27	1-9
A	DE,A,2 166 721 (THE UPJOHN CO.) 15 May 1975 Pages 1 and 12	1-6

* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1988-12-06	1988 -12- 27
International Searching Authority	**Signature of Authorized Officer**
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 10, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy.

2. [ ] Claim numbers ..., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.